REMARKS/ARGUMENTS

The Present Invention and the Pending Claims

Claims 1, 3-8, and 10-12 are pending. Claims 1 and 3-7 are directed to a method for producing a 5α-pregnane derivative represented by the formula (II). Claims 8 and 10-12 are directed to a method for producing (20S)-7α,21-dihydroxy-20-methyl-5α-pregn-3-one represented by the formula (IV).

Summary of the Claim Amendments

Claims 1 and 8 have been amended to delete a "hydroxyl-protecting group" from R^2, R^{12}, and R^{22}. Claims 1 and 8 also have been amended to recite the phrase "when R^3 and R^4 are each a hydrogen atom, the metal is present in an amount of 1.4-4 molar equivalents relative to the compound represented by the formula (I), and when R^3 and R^4 in combination form a bond, the metal is present in an amount of 2.8-8 molar equivalents relative to the compound represented by the formula (I)". This amendment is supported by the specification at, for example, page 13, lines 10-13 (and the underlying PCT patent application, WO 2005/095434, at, e.g., page 12, lines 4-9). Claims 2, 9, and 13-18 have been canceled. No new matter has been added by way of these amendments.

Summary of the Office Action

Claims 1-18 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description.

Claims 1-18 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nakazawa et al. (U.S. Patent Application Publication 2003/0181742) in combination with Moriarty et al. (*Tetrahedron Letters*, 35(44): 8103-8106 (1994)).

Reconsideration of the pending claims is hereby requested.

Discussion of the Indefiniteness and Written Description Rejections

Claims 1-18 allegedly are indefinite. The Office contends that the phrase "wherein the metal is present in an amount of 0.7-2 times the amount necessary for reducing the carbon-carbon double bond of the compound represented by formula (I)" is unclear because the quantities of the metal and compound of formula (I) are not recited. Without specifying the amount of the metal and compound of formula (I), the Office contends that it is not possible to determine the metes and bounds of the claims.

Claims 1-18 allegedly lack written description. According to the Office Action, the amount of metal necessary to reduce the carbon-carbon double bond of the compound of formula (I) is not disclosed in the specification. As a basis of the rejection, the Office points out that the working examples in the application describe a 5.05 molar excess (Example 1) and 2.20 molar excess (Example 2) of metal relative to the compound of formula (I). The Office contends that one cannot discern whether these amounts fall within the claimed range, and, as such, the specification lacks a written description of the claimed amount of metal ("wherein the metal is present in an amount of 0.7-2 times the amount necessary for reducing the carbon-carbon double bond of the compound represented by formula (I)").

As discussed above, claims 1 and 8 have been amended to recite the phrase "when R^3 and R^4 are each a hydrogen atom, the metal is present in an amount of 1.4-4 molar equivalents relative to the compound represented by the formula (I), and when R^3 and R^4 in combination form a bond, the metal is present in an amount of 2.8-8 molar equivalents relative to the compound represented by the formula (I)."

As illustrated in the Birch reduction mechanism, as described in the reference Bansal, R. K., *Synthetic Approaches in Organic Chemistry*, Hyde, C. W., Ed. (Jones and Bartlett: London, 1996), pages 113-114 (copy enclosed), it is well known that the theoretically required amount of the metal (electron source) in a Birch reduction is two molar equivalents per one carbon-carbon double bond.

$$Li + NH_3 \rightleftharpoons Li^+ \ldots e^- (NH_3)$$
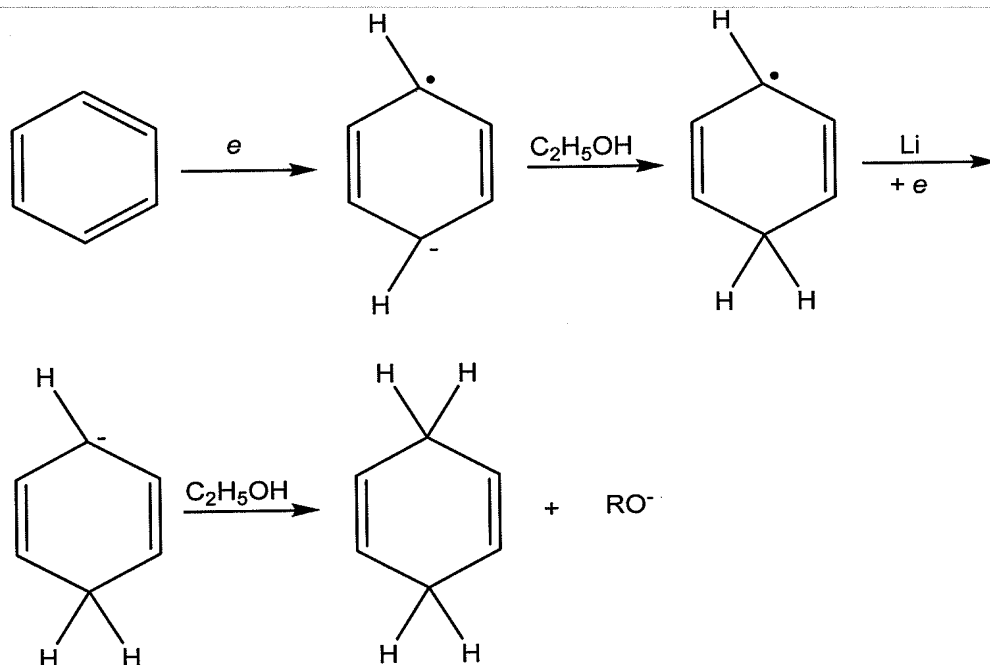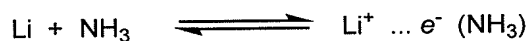
Therefore, one skilled in the art can easily understand that when R^3 and R^4 are each hydrogen (namely, the 1,2-position of the steroid is a single bond), such that the compound of formula (I) includes one double bond, "the amount necessary for reducing the carbon-carbon double bond of the compound (I)" is 2 molar equivalents relative to the compound of formula (I). When R^3 and R^4 in combination form a bond (namely, the 1,2-position of the steroid is a double bond), such that the compound of formula (I) includes two double bonds, "the amount necessary for reducing the carbon-carbon double bond of the compound (I)" is 4 molar equivalents relative to the compound of formula (I).

In Example 2, the amount of lithium (24 mmol) is 2.20 molar equivalents (2 x 1.10 = 2.20) relative to (20S)-21-tert-butyldimethylsilyloxy-7α -hydroxy-20-methylpregn-4-en-3-one (R^3 and R^4 are each a hydrogen atom (*monoene*), 10.9 mmol). Since, as explained above, 2.0 molar equivalents are needed in such a situation to reduce the single carbon-carbon double bond of the compound, the actual amount of metal utilized in Example 2 is 1.10 times the amount necessary for reducing the carbon-carbon double bond in the compound of formula (I). The value of 1.10 falls within the range of 0.7-2 times the amount necessary for reducing the carbon-carbon double bond of the compound represented by formula (I).

In Example 1, the amount of lithium (55 mmol) is 5.05 molar equivalents (4 x 1.26 = 5.05) relative to (20S)-21-tert-butyldimethylsilyloxy-7α-hydroxy-20-methylpregna-1,4-dien-3-one (R^3 and R^4 in combination form a bond (*diene*), 10.9 mmol). Since, as explained above, 4.0 molar equivalents are needed in such a situation to reduce the two carbon-carbon double bonds of the compound, the actual amount of metal utilized in Example 1 is 1.26 times the amount necessary for reducing the carbon-carbon double bond in the compound of formula (I). The value of 1.26 falls within the range of 0.7-2 times the amount necessary for reducing the carbon-carbon double bond of the compound represented by formula (I).

Claims 1 and 8 previously were amended to recite that the metal is present in an amount of 0.7 to 2 times the amount necessary for reducing the carbon-carbon double bond of the compound represented by formula (I) (specification at, e.g., page 13, lines 10-13; and the underlying PCT patent application, WO 2005/095434, at, e.g., page 12, lines 4-9). To clarify the amount of metal relative to the amount of the compound of formula (I), the range 0.7 to 2 has been amended to read molar equivalents. The following table describes the calculation underlying the amendment of the range of 0.7 to 2 times to a range of molar equivalents.

	molar equivalents of metal relative to the compound of formula (I) required	metal range: 0.7 to 2 times
Monoene	2	1.4 to 4 times (0.7x2) to (2x2)
Diene	4	2.8 to 8 times (0.7x4) to (2x4)

Thus, it is clear that the specification discloses the claimed ranges (1.4-4 and 2.8-8 molar equivalents of metal relative to the compound of formula (I)) both generally and specifically (see, e.g., specification at page 13, lines 10-13 and Examples 1 and 2; and the underlying PCT patent application, WO 2005/095434, at page 12, lines 4-9). Moreover, the amended claims more clearly recite the amount of metal to be added, since the recited ranges are in molar equivalents of the metal relative to the compound of formula (I). There is no doubt that one of ordinary skill in the art would be able to discern the quantities of both the metal and compound of formula (I) to be used in the context of the claimed invention as defined by the pending claims.

In view of the foregoing, Applicants submit that the amended claims are clear and definite and fully supported by the specification. As a result, Applicants respectfully request that the indefiniteness and written description rejections be withdrawn.

Discussion of the Obviousness Rejection

Claims 1-18 allegedly are obvious over Nakazawa et al. in combination with Moriarty et al. The reasons for the obviousness rejection are the same as provided in the previous Office Action.

Since claims 2, 9, and 13-18 have been canceled, the following discussion pertains to pending claims 1, 3-8, and 10-12.

The Office has already conceded that Nakazawa et al. does not disclose protecting the hydroxyl group(s) (e.g., R^1 in claims 1 and 8, and R^{21} in claim 8) prior to a reduction step, as required by the pending claims. Moriarty et al. describes protecting a 24-hydroxyl group but does not disclose a compound having a 7-hydroxyl group. In particular, Moriarty et al. discloses compound **5**, in which the 24-hydroxy group is protected with TBDMS (tert-butyldimethylsilyl), that was subjected to a Birch reduction using lithium and ammonia to give $5\bar{\alpha}$ steroid compound **6** in 81% yield. Compound **5** of Moriarty et al. does not have a 7-hydroxyl group, but rather has a 7-oxo group. See the following equation.
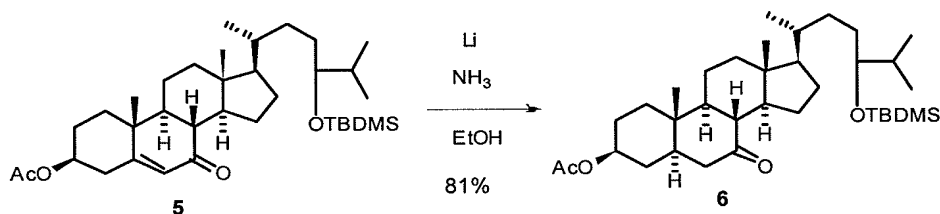
In contrast, Examples 1 and 2 in the present application achieve almost quantitative yields (e.g., 95% and 96%), which are 14-15% higher than that of Moriarty et al. In industrial processes, a quantitative yield is very advantageous because a potentially troublesome purification process can be avoided. Applicants speculate that the following reasons account for the surprising improvement in yield attendant the present invention.

In both Examples 1 and 2 of the present application, the 7α-hydroxy group is *not* protected (namely R^2 is a hydrogen atom). As discussed in the previous response, a Birch

reduction does not necessarily require the protection of a hydroxyl group, since the reaction requires a proton donor (e.g., an alcohol, an inorganic acid, water, etc.) (see specification at, e.g., page 14, lines 4-11). The 7α-hydroxy group itself can serve as a proton donor for a Birch reduction. As illustrated in the following putative reaction mechanism, the 7α-hydroxy group is considered to provide the intermediate 5-carbanion with a proton intramolecularly. In general, it is known that an intramolecular reaction proceeds far more rapidly and advantageously than an intermolecular reaction.

(I) R^2=H

tBuOH

5-carbanion

tBuOH

(II) R^{12}=H
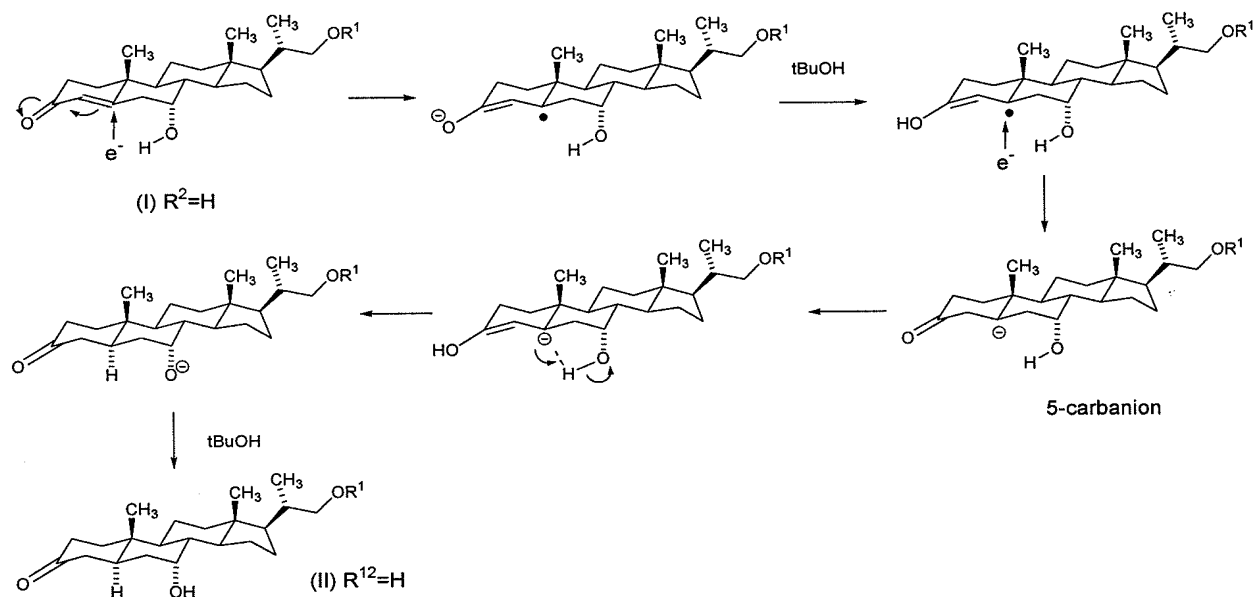
In addition, the 7α-hydroxy group could provide the 5-carbanion with a proton sterically-advantageously (from the α-face) to give the 5α-pregnane derivative as compared to an intermolecular reaction. In contrast, the 21-hydroxy group cannot provide the 5-carbanion with a proton intramolecularly due to steric distance, and, if anything, adversely affects such an intramolecular reaction (see the present specification at, e.g., page 3, lines 24-34).

Consequently, Applicants infer that the selective-protection of the 21-hydroxy group *without* protecting the 7α-hydroxy group contributes to the advantageous result of the present invention (i.e., quantitative or near quantitative yield). Accordingly, the claims have been limited to the embodiment in which the 7α-hydroxy group is not protected (i.e., R^2 is a hydrogen atom in claims 1 and 8, and R^{22} is a hydrogen in claim 8). Since compound **5** described in Moriarty et al. does *not* have an intramolecular hydroxyl group corresponding to

the present 7α-hydroxy group (rather, compound **5** has a 7-oxo group), the combination of Nakazawa et al. and Moriarty et al. does not teach or suggest the claimed method.
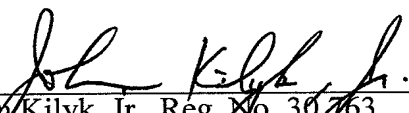
Moreover, neither Moriarty et al. nor Nakazawa et al. provides a credible reason for one of ordinary skill in the art to protect only a hydroxyl group at the 21-position prior to a Birch reduction. The Office contends that "[t]he issue here is whether the skilled artisan would have a reasonable expectation that the claimed reaction would run in the presence of [a] hydroxyl protecting group" (Office Action, page 5, third paragraph). In response, Applicants maintain that neither of the cited references appreciates nor recognizes the unexpected advantageous result (i.e., improved yield) of the present invention. A quantitative or near quantitative yield was unexpectedly discovered based on the method of the amended claims, and these results would not have been reasonably expected based on the disclosures of Nakazawa et al. or Moriarty et al. – either alone or in combination. Since such unexpected results can be achieved based on the methods defined by the amended pending claims, these unexpected results serve to rebut any *prima facie* obviousness rejection based on the combination of Nakazawa et al. and Moriarty et al.

In view of the foregoing, Applicants respectfully request that the obviousness rejection over Nakazawa et al. in view of Moriarty et al. be withdrawn.
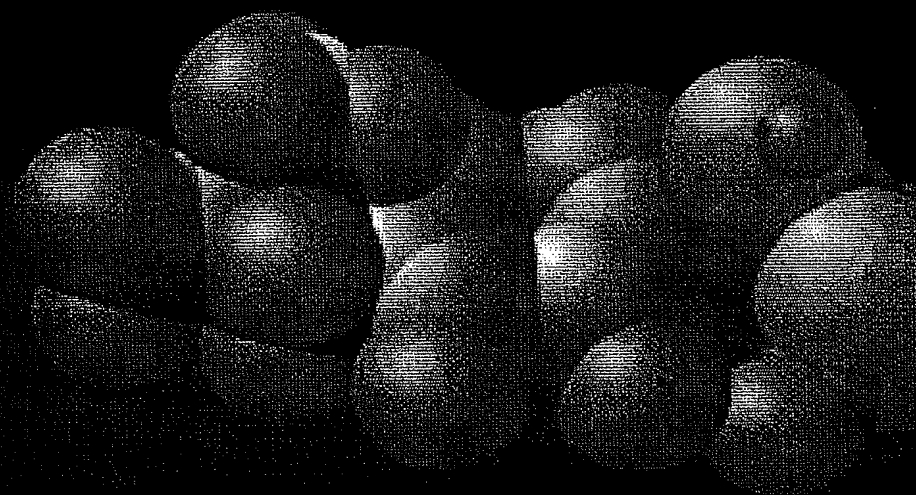
Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Synthetic Approaches in

ORGANIC CHEMISTRY

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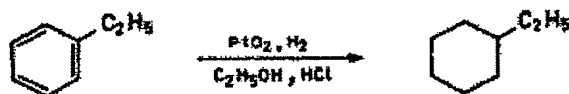
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metal hybrides reducing agents is that they are effective only for aromatic ketones, the aliphatic ketones are reduced with much lower optical purity.

2.2.3 The Birch Reduction

Aromatic rings can be completely reduced by catalytic hydrogenation.

Milder conditions are successful for hydrogenation with phase transfer catalysts.

But when aromatic rings are reduced by sodium or lithium in liquid ammonia (such reductions are known as dissolving metal reductions) and in the presence of ethanol or methanol (as proton donors) the aromatic ring is only partially reduced. This reaction is one of the most fundamental reactions in organic chemistry and is called the Birch reduction.[1,2] The reaction is usually conducted at the boiling point of ammonia (− 33°C). A familiar example involves the conversion of benzene to 1,4-dihydrobenzene in the presence of Na or Li/NH$_3$.
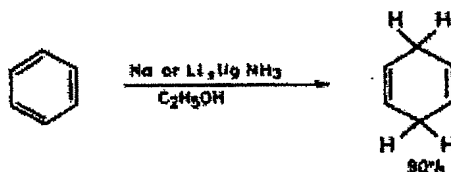
This reaction is initiated by electron transfer:

$$Li + NH_3 \rightleftharpoons Li^+ \ldots e^- \; (NH_3)$$

and an anion-radical is formed as an intermediate. The mechanism can be depicted in the following steps:

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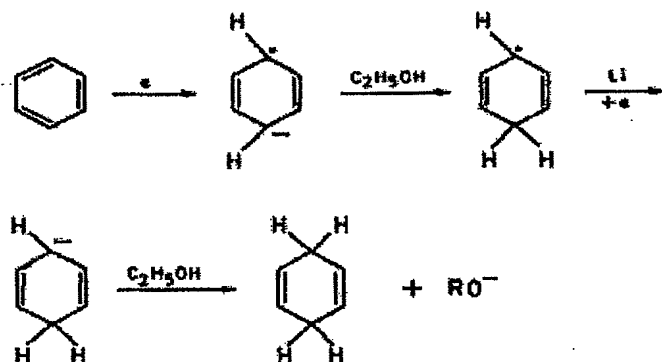
1. A.J. Birch, J. Chem. Soc., 430 (1944); for a review see, A.J. Birch, Quat. Rev., 4, 69 (1950).
2. For use in natural product synthesis, see J.M. Hooker and L.N. Mander, Natural Prod. Rep., 3, 35 (1986).

The mechanism of reduction involves, radical anion formation followed by protonation by an alcohol, addition of an electron and finally protonation of the cyclohexadienyl carbanion. The function of the donor is to protonate the intermediate anion-radical and thus to cut down on undesirable side-reactions such as dimerization of the radical anion and polymerization. The rate-limiting step is the protonation of the radical anion.[1] Birch reduction is used for the reduction of a wide variety of aromatic compounds varying in their degree of substitution and in the nature of substitution. The relative rates and regiochemistry are affected by the type of groups present on the ring. The substituents tend to stabilize or destabilize the radical anion[2]. Thus
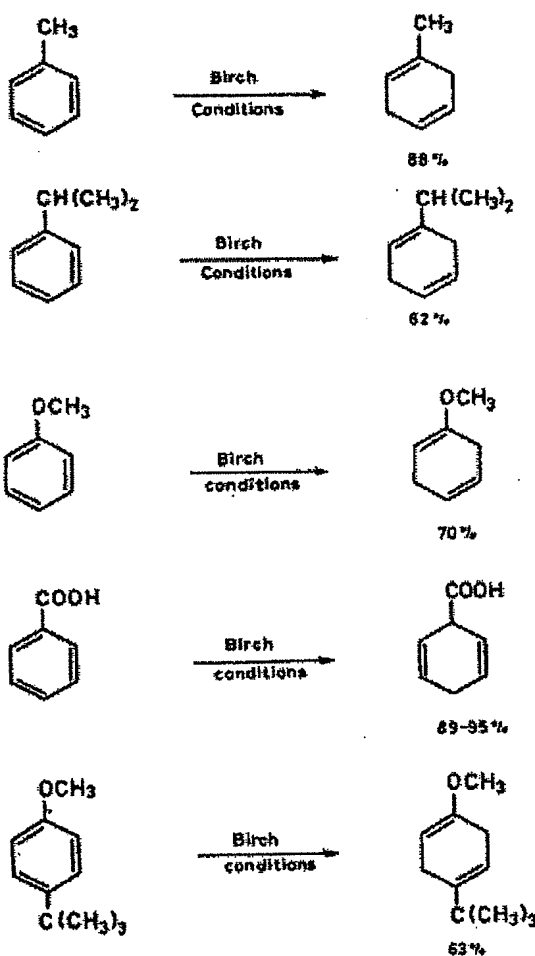
1. A.P. Krapcho and A.A. Bothner-By, J. Am. Chem. Soc., **81**, 3658 (1959).
2. P.W. Rabideau, Tetrahedron, **45**, 1579 (1989).